Therefore, support is provided for the lower range of 23.47 - 25.13.

As can be seen by the above discussion, the amended ranges are clearly supported by the preferred ranges wherein the errors are purely typographical in nature as seen from the non-overlapping ranges of the un-amended ranges.

Accordingly, Applicant respectfully requests entry and reconsideration and withdrawal of the objection to the amendment.

2. **Claim Objections**

The Office Action objects to the claims as being of improper dependent format. The Office Action states:

> Claims 25 and 27 are objected to under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claims(s) in proper dependent form, or rewrite the claim(s) in independent form. The TNF-α to IL-2 range of 7.7 to 11.3 does not include the limitations of the independent claims.

Applicant has amended claim 24 to recite the ratio range of TNF-α to IL-2 from "3.2 to 10.9" to "3.2 to 11.3". Support for the amendment can be found in the dependent claim 25, which was objected to as being in improper dependent format for containing

the larger range of "3.2 to 11.3". Accordingly, the range in dependent claim 25 has been amended to "3.2 to 10.9". Similar amendments were made with respect to independent claim 26 and dependent claim 27.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the objection to claims 25 and 27.

3. Rejection of Claims 24-27 under 35 U.S.C. § 102(b)

The Office Action rejects claims 24-27 under 35 U.S.C. § 102(b) as being anticipated over U.S. Patent No. 5,698,194 ("Hadden"). The Office Action states:

> US 5,698,194 ('194) teaches a serum free and mitogen free (column 5, lines 1-5) cytokine mixture *comprising* specific ratios of cytokines that encompass the following claimed ranges:
>
> IL-1β to IL-2 at a ratio range of 0.4 - 1.5, alternatively 036 to 1.5 (claims 25, 27);
>
> TNF-α to IL-2 at a ratio range of 3.2 - 10.9, alternatively 7.7 to 11.3;
>
> IFN-γ to IL-2 at a ratio range of 1.5 - 10.9, alternatively 4.9 to 7.1;
>
> GM-CSF to IL-2 at a ratio range of 2.2 - 4.8, alternatively 3.5 to 4.5.
>
> For example, (column 7, lines 23) GM-CSF ranges from 10-1500 pg/mL and IL-2 ranges from 100-500 units/mL. Thus, if the average amount

> of IL-2 is approximately 3000 units/mL, then the ratio of GM-CSF to IL-2 (10/300 and 1500/300) is .033 to 5 which encompasses the claimed ranges. Assuming the above, the prior art teaches the following range:
>
> IL-1 to IL-2 is .033 to 6.7
> TNF-α to IL_2 is .167 to 50
> IFN-γ to IL-2 is .167 to 50
> GM-CSF to IL-2 is .033 to 5
>
> The references further teach pharmaceutical compositions of the above cytokine mixture (column 10, line 10). Absence evidence to the contrary, it is assumed for examination purposes that the IL-1 used by the prior art was equivalent to and or comprised equivalent ratios of IL-1β.

Applicant respectfully traverses the rejection because Hadden does not teach each and every claimed limitation of the presently pending claims. Hadden fails to teach the proviso that IL-12 is present in only trace quantities. Instead, Hadden expressly teaches greater than trace amounts of IL-12 in the range of 100-10,000 pg/mL. See Hadden at col. 78, line 29. However, as stated in the Declaration filed on March 9, 2004, under § 1.132 by the inventor Dr. Eyal Talor, the presently claimed compositions only have trace amounts of IL-12 with a mean value of 42 pg/mL. Since the inclusion (and therefore exclusion) of different molecules imparts different functional and chemical distinctness, the presently claimed compositions are unanticipated by Hadden.

Turning to the rule, the Federal Circuit has held that

invention be disclosed in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Those elements must either be inherent or expressly disclosed and must be arranged as in the claim. In re Bond, 15 USPQ2d 1566 (Fed. Cir. 1990). Additionally, there must be no difference between the claimed invention and the reference disclosed, as viewed by a person of ordinary skill in the art. Richardson v. Suzuki Motor Co., 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989).

The prior art reference must also be enabling, thereby placing the allegedly disclosed matter in the possession of the public. In re Brown, 241 U.S.P.Q 245, 249 (C.C.P.A. 1964). In order to accomplish this, the reference must be so particular and definite that from it alone, without experiment or the exertion of his own inventive skill, any person versed in the art to which it pertains could construct and use it. Id. at 250.

Finally, the Federal Circuit has made clear that a negative pregnant is not enough to show anticipation. Rowe v. Dror, 42 U.S.P.Q.2d 1550 (Fed. Cir. 1997). Thus, where a reference does not explicitly describe anything inconsistent with a claimed use, if that reference nevertheless fails to make an affirmative suggestion of the claimed limitations, that reference cannot anticipate the claimed use. Id.

In the present application, independent claim 1 recites a serum-free and mitogen-free cytokine mixture, comprising:

specific ratios of cytokines selected from the group of IL-1β, TNF-α, IFN-γ and GM-CSF to Interleukin-2 (IL-2) as follows:

IL-1β to IL-2 at a ratio range of 0.4 - 1.5;

TNF-α to IL-2 at a ratio range of 3.2 - 11.3;

IFN-γ to IL-2 at a ratio range of 1.5 - 10.9; and

GM-CSF to IL-2 at a ratio range of 2.2 - 4.8

with the proviso that IL-12 is present in only trace quantities.

In contrast, Hadden expressly teaches greater than trace amounts of IL-12 in the range of 100-10,000 pg/mL. See Hadden at col. 78, line 29. Although Hadden teaches that the compositions are *comprising* the various components, it is clear the compositions of Hadden require IL-12 as a critical and necessary component. For example, Hadden teaches at col. 7, lines 24-34 that the cytokine profile of the composition is:

CYTOKINE	AMOUNT
IL-1	10-2000 pg/ml
IL-2	100-500 units/ml
IL-6	250-10,000 pg/ml
IL-8	12,000-100,000 pg/ml
IL-12	**100-10,000 pg/ml**
IFN-γ	50-15,000 pg/ml
TNF-α	50-15,000 pg/ml

CSF-G	50-1500 pg/ml
CSF-GM	10-1500 pg/ml
IL-3/IL-4/IL-7	Trace Amounts

Hadden goes on to show a specific embodiment wherein the composition contains IL-12 in amounts of 323 pg/ml and has only trace amounts of IL-3, IL-4, and IL-7. See Hadden at col. 8, lines 29-31. On the other hand, the presently claimed compositions only have trace amounts of IL-12 with a mean value of 42 pg/mL. Clearly, the claimed compositions are unanticipated by Hadden.

The claimed compositions are also unobvious because of the unexpected effect of pre-sensitizing cancer prior to a therapeutic treatment such as chemotherapy, radiation therapy or immuno-therapy.

Accordingly, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of the presently pending claims under § 102 over Hadden.

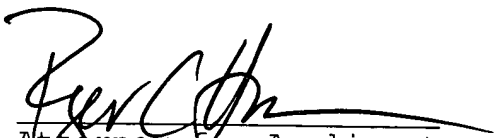
CONCLUSION

In light of the foregoing, Applicant submits that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of the pending claims and allow the pending claims.

Favorable action with an early allowance of the claims pending is earnestly solicited.

Respectfully submitted,

SHERMAN AND SHALLOWAY



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